RESPONSE TO OFFICE ACTION AND REMARKS

Applicants request entry of the amendments to the claims and specification. The amendment introduce no new matter. Amendments to the calims are not in reponse to any rejection on patentability. After entry of the amendments, claims 50 and 54-84 pending. Provision for 3-months extension of time accompanies this paper.

Restriction requirement

Applicants have amended Claim 50 and 62 to be within the scope of the Office's examination and to correct deficiencies. Amendment to Claim 50 provides the following definitions for R^1 through R^9.

R^1 is -OH, -SH, an ester, an ether, a thioester or a thioether;

R^2 is -H, -OH, -SH, an ester, an ether, a thioester or a thioether;

R^3 is -OH, =O, an ester, an ether, a thioester or a thioether;

R^4 is -OH, -SH, =S, an ester an ether, a thioester or a thioether;

R^5 is $-CH_3$ or $-CH_2OH$;

R^6 is -H, or $-CH_3$;

R^7 is $-CH_2-$ or $-CHR^{10}-$;

R^8 is $-CH_2$, -O- or -NH-;

R^9 is $-CH_2-$, $-CHR^{10}-$, -O- or -NH-; and

each R^{10} independently is -OH, an ester, an ether, -SH, a thioester, a thioether or a halogen

The definitions so provided define steroid nuclei with specific carbon-carbon bond connectivities and are thus deemed fully commensurate with the restriction requirement of the Office.

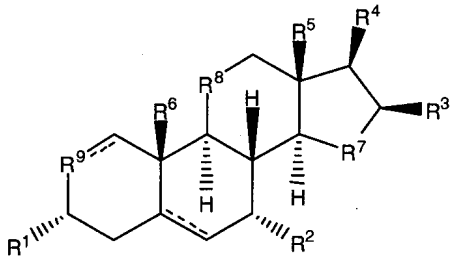
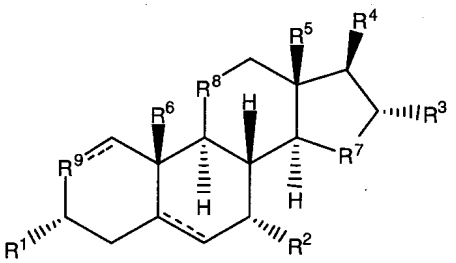
Objections to Specification

The Office objected to informalities, which are asserted to be on pages 89, 115, 137, 211 and 239. The overlapping structures on page 115 have been corrected by way of an amendment, which replaces the paragraph (para 00251) within which the overlapped structures appear. Applicants are uncertain as to the nature of the remaining objections for pages 89, 137, 211

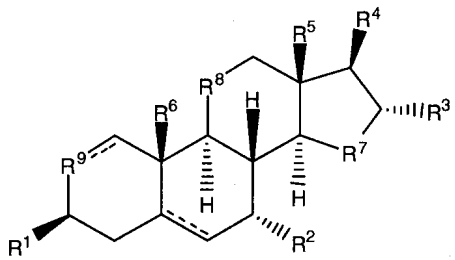
and 239. In order for the applicant to reply, clarity on the remaining objections to the specification is respectfully requested. Specifically, applicant requests a description of each objection and identification of paragraph and line where each objection occurs.

Objections to the Claims

The Office objected to Claims 66 and 67 as being in improper dependent form. Claims 50 and 62 have been amended to establish proper dependency of species listed in Claim 66, as currently amended, and in Claim 67. Written description support is present in the specification for the amendments to the claims. To facilitate the Office's written description review, a list of exemplary written description support for the currently amended claims is provided as follows.

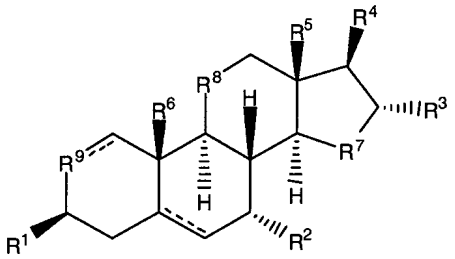
Claim	Support
50, 62, 68, 77	support for the R^1, R^2, R^3, R^4 $\alpha,\alpha,\beta,\beta$ compound structure  is present at embodiment 9A at paragraph 446, etc.
50, 62, 68, 77	R^1, R^2, R^3, R^4 $\alpha,\alpha,\alpha,\beta$ compound structure  embodiment 6A, paragraph 443, etc.
50, 62,	support for the R^1, R^2, R^3, R^4 $\beta,\alpha,\alpha,\beta$ compound structure

68



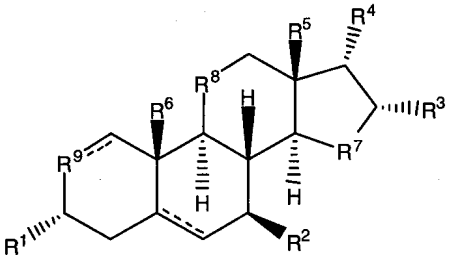
is present at embodiment 3A, paragraph 364 and compound group 38, paragraph 203, etc.

50, 62, 68 R^1, R^2, R^3, R^4 β,α,β,β compound structure



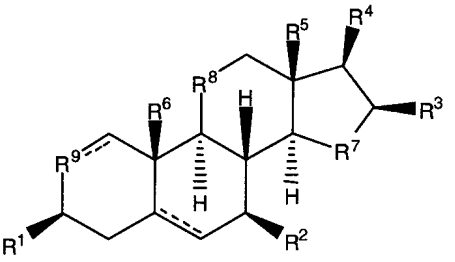
embodiment 9A, paragraph 446, etc.

62, 68 support for the R^1, R^2, R^3, R^4 α,β,α,α compound structure



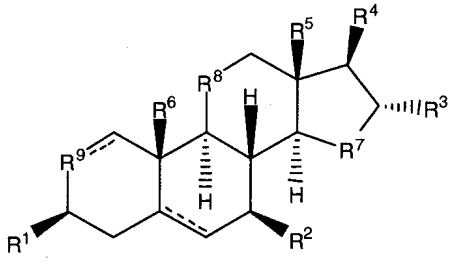
is present at embodiment 6A, paragraph 443, etc.

62, 68 R^1, R^2, R^3, R^4 β,β,β,β compound structure



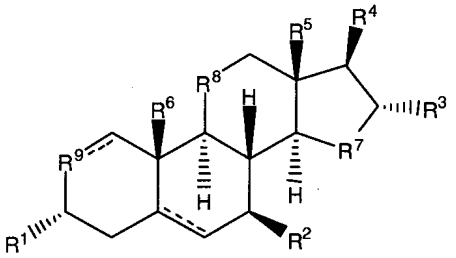
embodiment 9A, paragraph 446 and compound group 39, paragraph 204, etc.

62, 68 R^1, R^2, R^3, R^4 β,β,α,β compound structure



embodiment 3A, paragraph 364 and compound group 1, paragraph 156, etc.

62, 68 R^1, R^2, R^3, R^4 α,β,α,β compound structure



embodiment 6A, paragraph 443 and compound group 37, paragraph 202, etc.

66, 73 Support for 3α,16α,17β-trihydroxy-5α-androstane and 3α,17β-dihydroxy-5α-androstan-16-one is present in compound group 37, paragraph 202; and support for 3β-16α-17β-trihydroxy-5β-androstane is present in compound group 42, paragraph 207.

Claim Rejections - 35 USC §103

The Office has rejected Claims 50, 54, 55, 57-59, 61-64, 66, 67 and 77-84 in view of Dowel et al. (US 5,859,000), henceforth referred to as the '000 patent. Applicants object to citation of the '000 patent. The '000 patent had been previously considered by the Office as evidenced by Examiner's initials dated October 12, 2005 alongside the patent reference, which Applicant had provided in an IDS, received by the Office on June 15, 2005. Therefore, citation of the '000 patent at this stage of prosecution represents piecemeal examination, since the Office should have made its obviousness rejection based upon the '000 patent in its Final Office Action mailed October 21, 2005. In particular, 37 CRF 1.104 (b) states in part "The examiner's action will be complete as to all matters,

except that in appropriate circumstances...". Furthermore, MPEP 707.07(g) provides that "Piecemeal examination should be avoided as much as possible. The examiner ordinarily should reject each claim on all valid grounds available..." and MPEP 904.03, referenced within MPEP 707.07 (g), states "The examiner must *fully* (emphasis added) consider all the prior art references cited in the application, including those cited by the applicant in a properly submitted Information Disclosure Statement."

The Office is also reminded that examination normally proceeds beginning with an Applicants' elected species as given in the instant application in Claim 84 (method of treating asthma with 3α,16β,17β-trihydroxy-5α-androstane). Since the Office's obviousness analysis omits discussion of this compound and proceeds directly to species encompassed by genus claims, Applicants are uncertain as to the basis for rejection of Claim 84 and respectfully requests clarification.

In view of the foregoing and the failure of the Office to cite the '000 patent in a previous office action, Applicants respectfully requests the next office action on the merits be made non-Final.

Applicants traverse the 103(a) rejection. Applicants assert that hindsight bias has been employed by the Office in construction of the obviousness rejection and has failed to establish a *prima facie* case of obviousness for the use of the compounds of the instant invention for the treatment of asthma.

Hindsight Bias

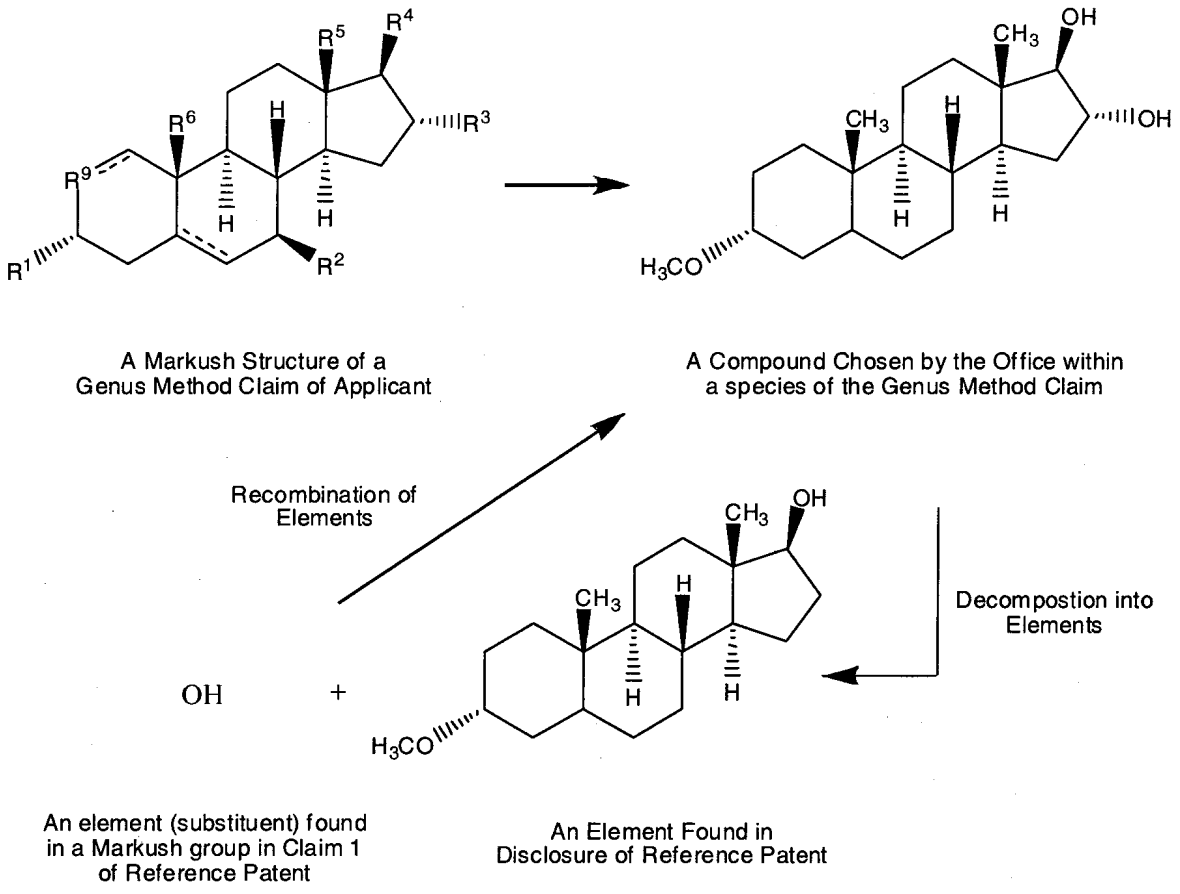
The history warning against hindsight bias is extensive as seen in the Supreme Court decision in *Diamond Rubber Co. v. Consolidated Tire Co.* (220 U.S. 428 (1911)). Particular warning against using an applicant's disclosure in constructing an obviousness rejection is found *in re Fritch*, 972 F.2nd 1260, 23 USPQ2d 1780 (Fed. Cir. 1992) which states "[I]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious". Of particular relevance is Judge Easterbrook's statement *in re Mahurkar Patent*

Litigation (831 F. Supp. 1354, 28 USPQ2d 1801 (N.D. Ill. 1993), aff'd, 71 F.3d 1573, 37 USPQ2d 1138 (Fed. Cir. 1995)) that "..decomposing an invention to its constitutive elements, finding each element in the prior art, and then claiming it is easy to reassemble these elements into the invention, is a forbidden ex post analysis". This is precisely what the Office has done.

The Office's has compared compounds contained within genus method claims in Applicant's invention to a list of fifty-four (54) compounds located in the specification of the '000 patent at col. 12, line 15 to col. 13 line 13. For each comparison the Office selected a compound from within a species of a genus method claim, decomposed the compound so as to obtain an element identical to a compound given in the list of the reference patent and then added to that element a substituent (element) listed in a Markush group found within a claim of that same reference to arrive at the compound that resides within the species encompassed by Applicant's genus claim. The following Scheme highlights the analysis and provides an example of the Office "decomposing an invention to its constitutive elements, finding each element in the prior art and then claiming it is easy to reassemble these elements into the invention". In this example, analysis by the Office supposedly arrives at 3α-ethoxy-16α,17β-dihydroxy-5α-androstane by removing the hydroxyl group at the 16-position of this compound, comparing the resulting element to the compound list of the reference patent, selecting 3α-ethoxy-5α-androstan-17β-ol, then adding to this element the hydroxyl substituent (element) to be found in a Markush group in Claim 1 of the reference patent.

However, recombination of the elements given in the aforementioned Scheme could also give 3α-ethoxy-16β,17β-dihydroxy-5α-androstane (with R^1, R^3, R^4 configuration of α,β,β), but the Office apparently has chosen the 16α configuration for the hydroxyl element to arrive at 3α-ethoxy-16α,17β-dihydroxy-5α-androstane (with R^1, R^3, R^4 configuration of α,α,β), based upon applicant's disclosure, presumably because the α,β,β stereochemical arrangement for the R^1, R^3, R^4 substituents had not appeared prior to the current amendment in a Markush structure of any of Applicants' examined claims. Therefore, the

obviousness analysis conducted by the Office would seem to be the epitome of hindsight bias.



For the Office's obviousness analysis using 16α-hydroxyl-5androsten-17-α-ol found within the list of the reference patent, a similar analysis apparently was used and relies upon addition of a α-hydroxyl group to the 3-position to reach a compound in a species contained within a genus claim of the Applicants and is thus similarly flawed. For the remaining example provided by the Office, Applicants are uncertain as to the relevance of "16α-methyl-16β-fluoro-5α-androsten-17-ol" (Applicants assume the Office is referring to 16α-methyl-16β-fluoro-5α-androstan-17-ol, since this compound is present in the compound list of the reference patent whereas the corresponding "adrosten" compound does not) to an obviousness assertion, since all compounds to be found within Applicant's

claims require mono-substitution at the 16-position. Therefore, Applicants respectfully request clarification as to the application of the remaining example to the 103(a) rejection to permit a response.

For the record instruction from the MPEP 8th Ed rev 5 in relation to hindsight bias is also noted and is provided immediately below.

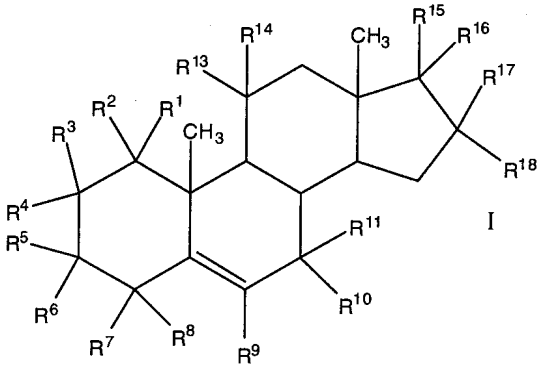
Failure to Establish a *Prima Facie* Case

2143 Basic Requirements of a *Prima Facie* Case of Obviousness

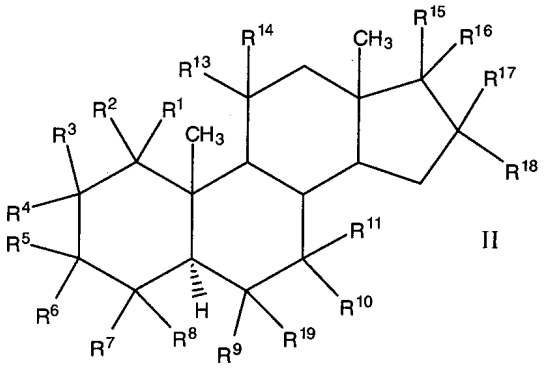
> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).
>
> *****

Claim 1 of the reference patent is the following.

1. A method of reducing mast cell mediated allergic reactions in a patient in need thereof which comprises administering to said patient an effective amount of a dehydroepiandrosterone (DHEA) derivative having the general formulas I and II and their pharmaceutically acceptable salts



I

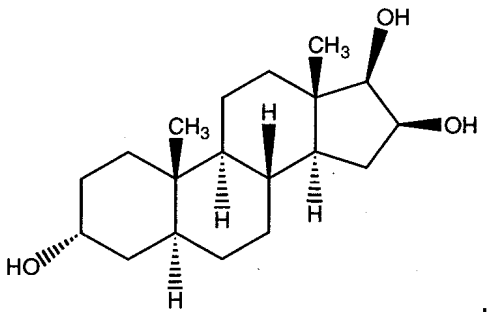


II

wherein (R group definitions omitted)

*****

Applicants' elected species is directed towards a method to treat or ameliorate asthma in a subject, comprising administering to the subject an effective amount of a compound having the structure



Firstly, it is noted that the Abstract of the '000 patent referred to by the Office contains a limitation to administering "in a manner which quickly raises blood levels of the active agent". Secondly, Formulas I and II contain 18 and 19 variable substituents (R^1 through R^{18}, R^{19}), respectively, with each R group substituent defined by a Markush group to provide hundreds of thousands if not millions of species and a multitude of subgenera which give rise to further species due to R group substituents within Markush groups that are defined by additional Markush groups and by variations in stereochemical relationships between the R^1 through R^{18}, R^{19} group substituents. In considering stereochemistry alone, Formula II has the potential to encompass 2^{14} distinct species (due to up to 9 carbon atoms bearing R group substituents and 4 carbon atoms of undefined stereochemistry within the 6-6-6-5 ring fused system) just for one single, distinct set of substituents.

Therefore, Claim 1 of the '000 patent encompasses many millions of species. From this vast array of compounds, the Office has not provided a rationale for a person having ordinary skill in the art to prepare the compound in Applicant's elected species (or for any other species in Applicants' claims) *in absence of the teaching in applicant's disclosure* much less shown, as will be

argued in due course, how the use of this compound would be obvious for the treatment of asthma.

In the event such a rationale can be provided with respect to a compound within one of Applicants' methods claims, it is noted for the record that in regards to a prior art chemical genus and a single chemical species, the court has observed that the "fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious. *In re Jones*, 958 F.2d 347, 350, 21 U.S.P.Q.2D (BNA) 1941, 1943 (Fed. Cir. 1992)". *In re Baird,* 29 USPQ2d 1550 1994. It is further noted the Office has failed to indicate where in the '000 patent itself is the actual suggestion to modify any one of the listed compounds at col. 12, line 15 - col.13, line 13 in the manner proscribed by the Office (quoting from *re Litner* 173 USPQ 560, 562 (CCPA 1972) ``In determining the propriety of the Patent Office case for obviousness in the first instance, it is necessary to ascertain whether or not the reference teachings would appear to be sufficient for one of ordinary skill in the relevant art having the references before him to make the *proposed substitution, combination or other modification* (emphasis added)" in order to arrive at the compound that is contained within the elected species of Claim 84.

Absence of motivation in the '000 patent to prepare the compound in Applicant's elected species (or for any other species in Applicants' claims) is further indicated by characterizion of the listed compounds relied upon by the Office as "[e]xamples of representative compounds which fall within the scope of general formulas I and II.." (col.12, lines 25-26). As a list of exemplary and not preferred compounds, there is no emphasis on any one compound and thus no guidance as to what modifications could be made to the compounds so listed. Furthermore, not one of the listed compounds has the 3, 16, 17-oxygen substitution pattern required by compounds in Applicants' claims and thus does not provide one having ordinary skill in the art motivation to make a compound with this substitution pattern for the purpose of treating a mast cell mediated allergic reaction.

The '000 patent discloses the ability of DHEA derivatives to "reduce or prevent mast cell mediated dependent reactions, including type I hypersensitivity response to allergens and asthma" as given in col. 13 lines 18-20. The claims of the '000 patent are all dependent on Claim 1 which encompasses "a method of reducing mast cell mediated allergic reactions". Indeed allergen exposure may trigger an asthma attack; however, as indicated in Col 5 lines 30-31 and lines 45-50 '[t]he mechanisms that induce all the pathological findings in asthma are not known" and "[t]here also appear to be antigen-independent mechanisms of inducing asthma, including viral infections and exercise. It is possible that these other mechanisms are also initiated by a common pathway of mast cell activation (*although many investigators believe mast cells are not of central importance (*emphasis added))". The '000 patent reference thus teaches away from the treatment of asthma outside of a mast cell mediated allergic reaction and introduces skepticism by practitioners having ordinary skill in the art that mast cells would be involved as a common mechanism in asthma without offering refuting evidence (notwithstanding Example 12 "Effect of a Single Dose of DHEAS on Exercise Induced Asthma in Human Volunteers" which is entirely prophetic). Quoting from *in re Peterson*, 315 F.3d 1325, 1331, 65 USPQ2d 1379 (Fed. Cir. 2003), "an applicant may rebut a prima facie case of obviousness by showing that the prior art teaches away from the claimed invention *in any material respect* (emphasis added)." and i*n re Haruna*, 249 F.3d 1327, 1335, 58 USQP2d 1517 (Fed. Cir. 2001) "A prima facie case of obviousness can be rebutted if the applicant ... can show `that the art in any material respect taught away' from the claimed invention"). Thus, the requirement *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). that "reasonable expectation of success must both be found in the prior art, not in applicant's disclosure" has not been met.

Therefore, Applicants asserts the Office has not established a *prima facie* case of obviousness for the treatment of asthma of every etiology using the compounds of the instant invention nor does it establish a *prima facie* case of obviousness for the compounds themselves.

Thus, in consideration of the foregoing, Applicants request withdrawal of the 103(a) rejection. Furthermore, Applicants request the next office action on the merits be non-Final and be complete as to all matters in order to expedite prosecution and that prosecution commence with the elected species of Claim 84.

Respectfully submitted,

Dated: December 01, 2006

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